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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,203	03/13/2002	Tracey Brown	650064.406USPC	8511

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EXAMINER

FUBARA, BLESSING M

ART UNIT	PAPER NUMBER
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1618

MAIL DATE	DELIVERY MODE
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08/28/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/889,203

Applicant(s)

BROWN, TRACEY

Examiner

Blessing M. Fubara

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 May 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 10-26 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 10-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Examiner acknowledges receipt power of attorney filed 12/20/06, request for extension of time, amendment and remarks filed 5/30/07. Claims 1-9 are canceled. New claims 10-26 are added and are pending.

Response to Arguments

Previous rejections that are not reiterated herein are withdrawn.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Claims 10, 11, 15 and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Falk et al. (US 5,985,850).

Falk discloses injectable formulations comprising anti-cancer agent or chemotherapeutic agent and hyaluronic acid (column 10, lines 8-59). The preferred molecular weight for the hyaluronan is less than 750,000 Daltons (claims 142, 83, 84 and 92). The anti-cancer drug or chemotherapeutic agent of Falk, specifically, methotrexate and 5-fluorouracil (claims 38 and 79) meet the drug and/or anti-neoplastic agent requirement of claims 10, 11, 15 and 16. The method of administration of the hyaluronan containing composition is by intravenous, intra arterially,

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intraperitoneally, intrapleurally, transdermally, topically, rectally, or by direct injection of the of the composition into a tumor (column 10, lines 48-55) and this administration meets the recited method of claim 10. Since the method of claim 10 administers the hyaluronan and drug composition to a patient to enhance the efficacy of a drug for a cancer cell, it flows that, when Falk administers the same composition to tumor site of a patient, the composition would inherently enhance the efficacy of the drug for cancer cell. Applicant's declaration, as previously noted, is not commensurate with 750 kDa. Thus, the demonstration provided in applicant's declaration has no data at the lower end of 750 kDa and the 30 kDa data is much lower than 750 kDa. Therefore, there is no conclusive factual evidence that molecular weight equal to 750,000 Dalton provides unusual and unexpected results. Therefore, the evidence provided does not support hyaluronic acid having molecular weight of equal to 750,000 Daltons as being inventive over the disclosure in the prior art of a molecular weight of less than 750,000. Falk anticipates the claims. However, in the, alternate, since Falk does not explicitly state that efficacy of a drug for a cancer cell is enhanced by administering a composition containing hyaluronan and anti-neoplastic agent or cytotoxic agent, it would be expected that the administration of the composition containing hyaluronan and anti-neoplastic agent or cytotoxic agent to a patient as described by Falk would provide the effect recited in the claims thereby rendering obvious the effect of enhancing the efficacy of a drug for cancel cell.

3. Claims 10 and 11 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Turley et al. (US 6,475,795 B1).

Turley discloses pharmaceutical composition that comprises anti-sense nucleic acid bound to hyaluronic acid for treating diseases or conditions treatable using gene therapy (column

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6, line 60 to column 7 line 10; column 2, line 62 to column 3 line 7 and claims 1-8). Turley specifically discloses that hyaluronan having a molecular weight of between 150,000 Daltons and 750,000 Daltons is preferred (column 7, lines 11-15 and 33; column 9, lines 37-40; claims 2 and 3). In column 7, line 64, hyaluronan having molecular weight of between 500,000 and 800,000 is used and larger molecular weight hyaluronan can be used in Turley except for hyaluronan having molecular weight exceeding 1,000,000 because at greater than 1,000,000, the hyaluronan self aggregates (column 10, lines 7-14). On the basis that Turley discloses larger molecular weight hyaluronan up to 1,000,000 but not exceeding, 1,000,000, there is then a disclosure for use of hyaluronan having molecular weight of greater than 750,000 and up to 1,000,000 Da in the formulation of Turley. Turley meets the limitations of the claims. However, in the, alternate, since Turley does not explicitly state that efficacy of a drug for a cancer cell is enhanced by administering a composition containing hyaluronan and cytotoxic agent, it would be expected that the administration of the composition containing hyaluronan and cytotoxic agent to a patient as described by Turley would provide the effect recited in the claims thereby rendering obvious the effect of enhancing the efficacy of a drug for cancer cell.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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5. Claims 10, 12-14, 17, 19-22, 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Falk et al. (US 5,985,850).

Falk discloses injectable formulations comprising anti-cancer agent or chemotherapeutic agent and hyaluronic acid (column 10, lines 8-59). The preferred molecular weight for the hyaluronan is less than 750,000 Daltons (claims 142, 83, 84 and 92). The anti-cancer drug or chemotherapeutic agent of Falk, specifically, methotrexate and 5-fluorouracil (claims 38 and 79) meet the drug and/or anti-neoplastic agent requirement of claims 10, 11, 15 and 16 as discussed above. The method of administration of the hyaluronan containing composition is by intravenous, intra arterially, intraperitoneally, intrapleurally, transdermally, topically, rectally, or by direct injection of the composition into a tumor (column 10, lines 48-55) and this administration meets the recited method of claim 10 as discussed above. Since the method of claim 10 administers the hyaluronan and drug composition to a patient to enhance the efficacy of a drug for a cancer cell, it flows that, when Falk administers the same composition to tumor site of a patient, the composition would inherently enhance the efficacy of the drug for cancer cell as discussed above.

The hyaluronate/hyaluronic acid used by Falk does not have a modal molecular weight of 890,000 Da or 750,000 Da. There is no demonstration in applicant's specification that a modal molecular weight of 890,000 or 750,000 Da provides unexpected results. Applicant's declaration, as previously noted, is not commensurate with 750 kDa. Thus, the demonstration provided in applicant's declaration has no data at the lower end of 750 kDa and the 30 kDa data is much lower than 750 kDa. Therefore, there is no conclusive factual evidence that molecular weight equal to 750,000 or 890,000 Dalton provides unusual and unexpected results. Therefore,

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the evidence provided does not support hyaluronic acid having molecular weight of equal to 750,000 or 890,000 Daltons as being inventive over the disclosure in the prior art of a molecular weight of less than 750,000.

While Falk prefers to use hyaluronic acid that has a molecular weight of less than 750,000 Da, Falk also teaches in the background that hyaluronic acid having molecular weight in exceeding 750,000 Da have effect in clinical symptoms of pain and swelling and also on the viscosity of composition. One of the goals of Falk is to provide formulations and conditions for delivery of medical and therapeutic agents for the treatment of diseases such as cancer (column 4, lines 20-25). Furthermore, Falk recognizes that the hyaluronic acid having molecular weights of 50,000 Da and upwards forms viscous solutions (column 4, lines 30-32). Claim 30 recites the property of the hyaluronan. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inject or administer by one of the means disclosed by Falk (column 10, lines 48-53) a composition comprising hyaluronic acid and anti-cancer agent to a subject in need thereof. One having ordinary skill in the art would have been motivated to use hyaluronic acid having the appropriate molecular weight that would provide formulations having the desired therapeutic effect and composition viscosity.

6. Claims 10, 11, 18, 20 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Falk et al. (US 5,985,850) in view of Broder et al. (US 5,968,972).

Falk has been discussed above to anticipate or render obvious claims 10 and 11, and has also been discussed to render obvious claim 20. While the formulation of Falk contains methotrexate and/or 5-fluorouracil as anti-neoplastic agents, paclitaxel is not one of the anti-neoplastic agents present in the formulation. However, paclitaxel is a known anti-cancer or anti-

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neoplastic drug as described in the abstract of Broder. One antineoplastic agent can be used in place of the other and expect to a formulation that has anti-cancer effect. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made formulate and use the composition of Falk that contains hyaluronic acid and methotrexate or 5-fluorouracil and also to use other anti-neoplastic agents such as paclitaxel with the expectation that the composition containing the paclitaxel would also have anti-cancer activity when administered.

Response to Arguments

7. Applicant's arguments filed 5/30/07 as the arguments relate to the new claims and the new rejections have been fully considered but they are not persuasive.

Applicant argues a) that the original specification supports molecular weight greater than 750 Da; b) that Falk does not teach or suggest that administration of HA with an anti-cancer agent reverses or overcomes resistance of cancer cells to anti-cancer agent or overcomes drug resistance as recited in claim 10.

Response:

Page 17, line 37 and page 29 line 28 supports a single molecular weight of 890,000 Da. However, regarding a) the argument is moot in view of the new claims and the limitation of specific molecular weights of 750,000 and 890,000 Da in the dependent claims. Regarding b), the method of claim 10 requires enhancing efficacy of a drug for a cancer cell, which is resistant to said drug, the method comprises administering a hyaluronan and said drug. Therefore, for claim 10, it is the administering of the hyaluronan and the drug that leads to the enhancement of the efficacy of the drug for the cancer cell. Falk also administers hyaluronan and anti-cancer

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agents that are the same as those anti-cancer agents specifically recited in claims 15, 16, 21, 22, 25 and 26 so that the effect of the formulation would inherently be the same

8. Claims 10-26 are rejected under in the alternative, under 35 U.S.C. 103(a) as obvious over Turley et al. (US 6,475,795 B1) in view of Buckbinder et al. (US 5,840,673) or Johnson et al. (US 6,087,350).

Turley is discussed above as anticipating or in the alternative rendering obvious claims 10 and 11. Turley discloses pharmaceutical composition that comprises anti-sense nucleic acid bound to hyaluronic acid for treating diseases or conditions treatable using gene therapy (column 6, line 60 to column 7 line 10; column 2, line 62 to column 3 line 7 and claims 1-8). Turley specifically discloses that hyaluronan having a molecular weight of between 150,000 Daltons and 750,000 Daltons is preferred (column 7, lines 11-15 and 33; column 9, lines 37-40; claims 2 and 3). In column 7, line 64, hyaluronan having molecular weight of between 500,000 and 800,000 is used and larger molecular weight hyaluronan can be used in Turley except for hyaluronan having molecular weight exceeding 1,000,000 because at greater than 1,000,000, the hyaluronan self aggregates (column 10, lines 7-14). On the basis that Turley discloses larger molecular weight hyaluronan up to 1,000,000 but not exceeding, 1,000,000, there is then a disclosure for use of hyaluronan having molecular weight of greater than 750,000 in the formulation of Turley. There is a disclosure for composition comprising hyaluronic acid having molecular weight of 500,000 to 800,000 or to 1,000,000 Daltons and a composition that may have hyaluronan having preferred molecular weight of between 15,000 and 750,000 Daltons. Since molecular weight of 500,000 Daltons to 1,000,000 Daltons encompasses molecular

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weights of 750,000 and 890,000 Da, Turley renders obvious a molecular weight of 750,000 and 890,000 Daltons, and thereby renders obvious claims 12-14, 17-20 and 24; molecular weight of 750,000 and 890,000 Da are not inventive over the prior art. The declaration submitted by applicant is not commensurate with the claims.

Turley discloses anti-sense nucleic acid as the cytotoxic agent. Turley does not disclose non-polynucleic acid based cytotoxic agent as recited in claims 15, 16-19, 21-23, 25 and 26. But one cytotoxic agent can be used in place of another with the expectation of producing antineoplastic effect. Buckbinder (claim 4) and Johnson (column 6, lines 53-64) recognize paclitaxel, methotrexate, 5-fluorouracil, cisplatin, cyclophosphamide and camptothecin as cytotoxic agents. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inject a composition comprising hyaluronic acid and anti-sense agent to a subject in need thereof. One having ordinary skill in the art would have been motivated to use other cytotoxic agents such as paclitaxel, methotrexate, 5-fluorouracil, cisplatin, cyclophosphamide and camptothecin as cytotoxic agents in place of the anti-sense nucleic acid with the expectation that these substitutes will provide anti-neoplastic or cytotoxic effect.

Response to Arguments

9. Applicant's arguments filed 5/30/07 as the arguments relate to the new claims and the new rejections have been fully considered but they are not persuasive.

Applicant argues a) that Turley uses HA as a targeting agent for gene therapy; b) that Turley does not provide data or suggestion or teaching that the use of HA when combined with an anticancer agent would reverse or overcome the resistance of cancers

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to the anti-cancer agent; c) that Examples 1-3 demonstrate the effect of irinotecan with HA on colon cancer (Example 1), combination of methotrexate and HA on breast cancer cell and colon cancer cell line (Examples 2 and 3), combination of HA and cytotoxic agents reduced acquired resistance to 5-FU and irinotecan or doxorubicin (Example 4) and that Turley had failed in this respect and as such the rejections should be withdrawn.

Response:

Regarding a) it is noted that the property of HA cannot be separated from it and as such HA would provide its inherent property when administered. Regarding b), the method of claim 10 requires enhancing efficacy of a drug for a cancer cell, which is resistant to said drug, the method comprises administering a hyaluronan and said drug. Therefore, for claim 10, it is the administering of the hyaluronan and the drug that leads to the enhancement of the efficacy of the drug for the cancer cell. Turley also administers hyaluronan and cytotoxic agent. HA is well known in the art and “[t]he discovery of a previously unappreciated property of prior art composition, or of a scientific explanation for the prior art’s functioning, does not render the old composition patentably new to the discoverer.” *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property, which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). Thus, because what the HA does is an inherent function of this well-known compound, the prior art does not have to disclose all the function of a known compound. Regarding c), limitations from the specification cannot be imported into the claims. The data in the examples are not commensurate with limitations of the claims.

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No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 7571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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